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IN THE

Supreme Court of the United States

LABORATORY CORPORATION OF AMERICA HOLDINGS (DOING BUSINESS AS LABCORP),

Petitioner,

v.

METABOLITE LABORATORIES, INC. AND COMPETITIVE TECHNOLOGIES INC.,

Respondents.

On Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

BRIEF FOR THE AMERICAN MEDICAL ASSOCIATION, THE AMERICAN COLLEGE OF MEDICAL GENETICS, THE AMERICAN COLLEGE OF OBSTETRICIANS AND GYNECOLOGISTS, THE ASSOCIATION FOR MOLECULAR PATHOLOGY, THE ASSOCIATION OF AMERICAN MEDICAL COLLEGES, AND THE COLLEGE OF AMERICAN PATHOLOGISTS AS *AMICI CURIAE* IN SUPPORT OF PETITIONER

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QUESTION PRESENTED

Whether a method patent setting forth an indefinite, undescribed, and non-enabling step directing a party simply to "correlat[e]" test results can validly claim a monopoly over a basic scientific relationship used in medical treatment such that any doctor necessarily infringes the patent merely by thinking about the relationship after looking at a test result.

TABLE OF CONTENTS

	Page
QUESTION PRESENTED	i
TABLE OF AUTHORITIES	iv
INTRODUCTION AND INTEREST OF *AMICI CURIAE*	1
MEDICAL AND ETHICAL BACKGROUND	6
A. The Nature Of And Tests For Homocysteine	7
1. Early Research Into Homocysteine And Its Association With Disease	8
2. Importance Of Tests For Homocysteine	9
3. Current Use Of Homocysteine Tests And Research Into Homocysteine	11
B. Ethical Concerns With Patents On Scientific Principles	13
SUMMARY OF ARGUMENT	15
ARGUMENT	16
A. Claim 13 Improperly Claims Non-Patentable Subject Matter	16
B. Claim 13 Is Overbroad	21
C. Patents Solely On Scientific Facts Stifle Innovation And Conflict With Patient Care	23
CONCLUSION	27

TABLE OF AUTHORITIES

CASES — Page

62 Cases of Jam v. *United States*, 340 U.S. 593 (1951) 26
Diamond v. *Chakrabarty*, 447 U.S. 303 (1980) 16, 17
Diamond v. *Diehr*, 450 U.S. 175 (1981) 17, 19
Funk Bros. Seed Co. v. *Kalo Inoculant Co.*, 333 U.S. 127 (1948) 23
In re Hyatt, 708 F.2d 712 (Fed. Cir. 1983) 21
LeRoy v. *Tatham*, 55 U.S. (14 How.) 156 (1852) . 17, 20
Mackay Radio & Tel. Co. v. *Radio Corp. of Am.*, 306 U.S. 86 (1939) 19, 20
Morton v. *New York Eye Infirmary*, 17 F. Cas. 879 (C.C.S.D.N.Y. 1862) (No. 9865) 19, 20
O'Reilly v. *Morse*, 56 U.S. (15 How.) 62 (1853) 21, 22, 24
Wyeth v. *Stone*, 30 F. Cas. 723 (C.C.D. Mass. 1840) (No. 18,107) 21

CONSTITUTION AND FEDERAL STATUTES

U.S. Const. art. I, § 8, cl. 8 16
Act of Feb. 21, 1793, ch. 11, 1 Stat. 318 16
Act of July 19, 1952, ch. 950, 66 Stat. 792 17
35 U.S.C. § 101 2
§ 112 18
§ 287(c) 25

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S. Rep. No. 82-1979 (1952), *reprinted at* 1952 U.S.C.C.A.N. 2394 17
H.R. Rep. No. 82-1923 (1952) 17

PATENT

U.S. Patent No. 4,940,658 (filed Nov. 20, 1986) .. 10, 15

TABLE OF AUTHORITIES – continued

SCHOLARLY AUTHORITIES Page

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Page

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Page

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Page

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TABLE OF AUTHORITIES – continued

Page

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INTRODUCTION AND INTEREST OF *AMICI CURIAE*[1]

Since the time of Hippocrates, a basic tenet of medical ethics has been that discoveries and advances in medical care should be freely shared and openly disseminated. This ethical principle has served to make such discoveries readily available, at minimal cost, for use in the diagnosis and treatment of patients. It also has helped physicians fulfill their fundamental obligation to act in their patients' best interests.

For more than 200 years, the patent laws have, with few exceptions, existed in harmony with the professional ethical duty to publish and disseminate medical advances. Misapplication of the patent laws by the lower courts in this case, however, has created tension with basic principles of medical ethics. This would not have occured if the patent laws had been construed consistently with this Court's precedent.

Specifically, the Federal Circuit has held that Claim 13 of the patent at issue in this case gives the patentees exclusive private ownership not of a new drug, or of a new diagnostic test, or even of a new method of diagnosing a particular disease – but rather of a scientific fact. Claim 13 covers any "correlation," construed by the lower court as merely an "association" or "conclusion" in a physician's mind, between (a) a test result – however obtained – for blood levels of homocysteine and (b) a vitamin deficiency. Claim 13 is thus infringed whenever a physician, having ordered a test (patented or not), reviews the test results with the relationship between homocysteine and vitamin deficiency in mind.

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[1] Pursuant to Rule 37.6, *amici* state that no counsel for any party drafted this brief in whole or in part, and no persons or entities other than *amici* made any monetary contribution to its preparation or submission. Letters of consent have been filed with the Clerk.

The scope of patentable subject matter as established by Congress in the Patent and Trademark Act ("the Act"), although quite broad, does not extend to a physician's consideration of a scientific fact. A patient's elevated levels of the amino acid homocysteine may well indicate a vitamin deficiency. That a physician thinks of that relationship when reviewing laboratory test results, however, is not evidence that the physician is engaging in a "process," as that term is used in Section 101 of the Act, 35 U.S.C. § 101. Rather, it is evidence only that a physician is aware of a pre-existing scientific relationship.

Once recognized, the relationship between elevated homocysteine levels and a potential vitamin deficiency cannot be ignored. Such a fact should be used in the diagnosis and treatment of patients and publicized in order to advance medical science. Properly construed, Section 101 of the Act does not interfere with the spread and use of such information, because allowing a physician to think about the relationship between a test result and a patient's physical condition is not a patentable "process" within the meaning of Section 101.

Of course, if the basic fact that certain test results correlate with a given physical condition were to be incorporated into some useful application, then that application might be a patentable advance over prior art. But the fact of the correlation alone is not, under Section 101, subject matter eligible for patent protection. It therefore cannot, in itself, provide a valid basis for enjoining a laboratory from performing tests – or for discouraging laboratories from providing physicians with information about the significance of test results that physicians can then use in the diagnosis and treatment of patients.

The Federal Circuit's construction of Claim 13 contravenes limitations on the scope of patentable subject matter that have existed for more than two centuries. If affirmed, it will permit patentees to restrict access to, and use of, basic scientific

principles. Allowing a private party to enforce a patent on a scientific fact prevents physicians from exercising their best medical judgment in treating their patients and thereby inhibits the sound practice of medicine. On behalf of their hundreds of thousands of members nationwide, the medical associations that are submitting this brief urge the Court to enforce the limitations imposed by the Act on the subject matter of patents.

The American Medical Association (AMA) is a private, voluntary non-profit organization of physicians and medical students with approximately 250,000 members, who practice in all states and in all fields of medical specialization.[2] The AMA was founded in 1847 to promote the science and betterment of public health. From its inception, the AMA has maintained a Code of Medical Ethics, including a set of core Principles and a Code and Opinions applying those Principles, which guide the ethical practice of medicine. Several of these principles and opinions, as well as reports of the AMA's Council on Ethical and Judicial Affairs, address ethical issues raised by the issuance of patents on medically useful information.[3]

The American College of Medical Genetics (ACMG) is a private, non-profit, voluntary organization of clinical and laboratory geneticists. The Fellows of the ACMG are doctoral level medical geneticists and other physicians involved in the practice of medical genetics. The 1,300 members of the ACMG practice in all states. The ACMG promotes the development and implementation of methods to

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[2] The AMA submits this brief on its own behalf and as a representative of the Litigation Center of the American Medical Association and the State Medical Societies. The Litigation Center is a coalition of the AMA and the medical societies of every state and of the District of Columbia, formed to represent the views of organized medicine in the courts.

[3] *See, e.g.*, Am. Med. Ass'n, *Patenting of Medical Procedures*, 53 Food & Drug L.J. 341 (1998).

diagnose, treat and prevent genetic disease. In order to fulfill this mission, the ACMG strives to 1) advance the art and science of medical genetics by maintaining high standards in education, practice and research; 2) increase access to medical genetic services and improve public health; 3) develop clinical practice guidelines; and 4) establish uniform laboratory standards, quality assurance and proficiency testing. The position of the ACMG is that naturally occurring substances should not, in and of themselves, be patentable.

The American College of Obstetricians and Gynecologists (ACOG) is a non-profit educational and professional organization founded in 1951. With more than 45,000 members in the United States, ACOG is the leading professional association of physicians who specialize in the health care of women. ACOG was established to foster and stimulate improvements in all aspects of the health care of women; to establish and maintain the highest possible standards for education; to foster the highest quality of practice; to promote high ethical standards in practice; to promote publications and encourage contributions to medical and scientific literature. ACOG has over forty standing committees to carry out its mission, including the Committee on Ethics. In November 2002, ACOG published a Committee Opinion addressing patents, medicine and the interests of patients.[4]

The Association for Molecular Pathology (AMP) is an international not-for-profit scientific education society representing over 1,300 physicians, doctoral scientists, and medical technologists who perform molecular diagnostic testing based on the applications of genomics and proteomics. AMP is committed to the advancement of clinical molecular diagnostic and prognostic medicine through education and

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[4] *See* Am. Coll. of Obstetricians & Gynecologists, *Patents, Medicine, and the Interests of Patients, in Ethics in obstetrics and gynecology* (ACOG Washington, D.C. 2d ed. 2004).

training of practitioners, physicians, laboratory and industrial scientists, and health care professionals involved in patient care and management. AMP supports the development of new technologies in molecular biology to be used in laboratory medicine, including diagnosis, treatment, and prognosis of genetic disorders, cancer, infectious diseases, identity and histocompatibility. AMP members are involved in every aspect of molecular diagnostic testing, administration and interpretation of molecular diagnostic tests, research and development, and education. AMP provides national leadership for the advancement of safe and effective practice and education for molecular diagnostic testing in the health care industry. In November 1999, AMP adopted a position statement opposing patents and licensing agreements that inappropriately limit clinical care, the use of medical procedures, medical education, and medical research.

The Association of American Medical Colleges (AAMC) is a non-profit organization representing all 125 allopathic medical schools in the United States, about 400 major teaching hospitals and health systems, and 94 academic and professional societies representing nearly 110,000 faculty members. AAMC's member institutions are at the forefront of medical education, research and research training, and health care innovation and delivery. AAMC members perform nearly 60% of the extramural research sponsored by the National Institutes of Health, and they partner with industry in discovering new and better approaches to the diagnosis, treatment, and prevention of human diseases. The AAMC is committed to the continuing improvement of health care and the Continuing Medical Education of physician practitioners based on sound scientific evidence. These goals require, and AAMC strongly supports, policies that promote the unfettered generation and dissemination of new scientific knowledge, the transfer of new technologies from university laboratories to social and commercial application, and the broadest possible sharing of scientific and medical

information in support of the advancement of science, patient care, and the health of the public.

The College of American Pathologists (CAP) has nearly 16,000 physician members, including 91% of all eligible board-certified pathologists. It is the world's largest medical society composed exclusively of pathologists, who are physicians who obtain and interpret data as the result of examination of tissues, blood, and other body fluids for diagnosis and patient care. The CAP also serves the laboratory community throughout the world. More than 6,000 laboratories are accredited by the CAP, and approximately 23,000 laboratories are enrolled in the College's proficiency testing programs.

MEDICAL AND ETHICAL BACKGROUND

The patent in this case, United States Patent No. 4,940,658 (the '658 patent), sets forth a method of testing for blood levels of the amino acid homocysteine using gas chromatography and mass spectrometry. The inventors used this method to study a correlation between elevated homocysteine and vitamin deficiencies. The results of their testing for this correlation are reported in the patent.

To assist this Court in understanding the '658 patent and how the enforcement of Claim 13 would negatively affect medical care and research, amici offer the following medical background. As this background will demonstrate, the test methods and scientific observations in the '658 patent did not emerge in a vacuum. They are part of a continuum of medical research and development aimed at improving patient care. Amici believe that the enforcement of a broad and unwarranted patent claim on the association between elevated levels of homocysteine and vitamin deficiencies would interfere substantially with the achievement of that goal and would raise important ethical issues.

A. The Nature Of And Tests For Homocysteine

Homocysteine is an amino acid[5] that is normally found in very small amounts in human blood, where it exists in multiple forms.[6] Well before the filing of the application for what became the '658 Patent, researchers understood the critical role of vitamins B_6, B_{12} (cobalamin) and folate (folic acid) in the metabolism of homocysteine and the impact of an individual's dietary intake of these vitamins on homocysteine levels.[7]

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[5] An amino acid is an organic compound containing an amino (NH_2) and a carboxyl (COOH) group. In the human body, amino acids are linked together to form proteins. An "essential" amino acid is one that is required for protein synthesis but cannot be made by humans and, therefore, must be supplied in the diet. *Dorland's Illustrated Medical Dictionary*, *available at* http://www.mercksource.com/pp/us/cns_hl_dorlands.html (last visited Dec. 14, 2005).

[6] Those forms include protein-bound homocysteine (about 70%), free homocysteine, the disulfide homocystine, and mixed homocysteine-cysteine disulfide. Together, these forms are referred to as total plasma (or serum) homocysteine, or as total homocysteine, [hereinafter "homocysteine"]. Am. Soc'y of Human Genetics/Am. Coll. of Med. Genetics, *Measurement and Use of Total Plasma Homocysteine*, 63 Am. J. Hum. Gen. 1541 (1998), *reaffirmed* by Am Coll. of Med. Genetics (Oct. 25, 2005).

[7] In humans, homocysteine is formed as an intermediary during the conversion of the essential amino acid methionine to the amino acid cysteine. In this metabolic pathway, in which homocysteine is both created and largely reconverted back to methionine, vitamins B_{12} and folate (as well as other enzymes and coenzymes) play a critical role. Impaired reactions in this pathway, because of defects in the required enzymes or the vitamin coenzymes, may result in an increased accumulation of homocysteine in the blood. *See generally* L.D. Fleisher & G.E. Gaull, *Methionine Metabolism in Man: Development and Deficiencies, in* 3 *Clinics in Endocrinology and Metabolism* 36 (H. Bickel ed., 1974). *See also* M.C. Higgenbottom, L. Sweetman & W.L. Nyhan, *A syndrome of methylmalonic aciduria, homocystinuria, megaloblastic anemia and neurological abnormalities in a vitamin B_{12}-deficient breast-fed infant of a strict vegetarian*, 299 N. Eng. J. Med. 317 (1978); D.A.

1. Early Research Into Homocysteine And Its Association With Disease

In 1963, an association between elevated homocysteine levels and human disease was shown by a finding of very high homocystine/homocystine concentrations in the urine of some children with mental retardation.[8] This condition, called homocystinuria, was shown to be caused by an inherited enzymatic error of homocysteine metabolism.[9] Among the clinical effects of this disorder was the occurrence of premature occlusive cardiovascular disease.

In 1969, Dr. Kilmer McCully described the vascular pathology in homocystinuria patients and suggested that the vascular damage was produced specifically by the accumulation of homocysteine or its derivatives.[10] During the next fifteen years, it was discussed and well documented that even a moderately elevated level of homocysteine is a strong independent risk factor for heart disease and stroke.[11]

By 1969, at least two articles had reported that elevated levels of homocyst(e)ine could result from a deficiency of vitamin B_{12}.[12] It also was shown, however, that the etiologies

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Hollowell et al., *Homocystinuria and organic aciduria in a patient with vitamin B_{12} deficiency*, 2 Lancet 1428 (1969).

[8] N.A.J. Carson et al., *Homocystinuria: a new inborn error of metabolism associated with mental deficiency*, 38 Arch. Dis. Child. 425 (1963).

[9] *Id.*

[10] K. McCully, *Vascular pathology of homocystinuria: Implications for the pathogenesis of arteriosclerosis*, 56 Am. J. Pathol. 111 (1969).

[11] *See, e.g.*, L.B. Brattstrom et al., *Moderate homocysteinemia – A possible risk factor for arteriosclerotic cerebro-vascular disease*, 15 Stroke 1012 (1982). K.S. McCully, *Homocysteine theory of arteriosclerosis: Development and current status*, 11 Atherosclerosis Rev. 157 (1983).

[12] Hollowell et al., *supra* note 6. M.C. Carey et al., *Homocystinuria. II. subnormal serum folate levels, increased folate clearance and effects of folic acid therapy*, 45 Am. J. Med. 26 (1968).

of elevated plasma homocysteine ("homocysteinemia" or "hyperhomocysteinemia") are complex and that several factors, both genetic and environmental, may contribute to elevated plasma homocysteine levels, even if an individual's vitamin intake is normal. These factors include chronic renal disease, alcoholism, drug-induced effects, and several different genetic abnormalities.[13]

2. Importance Of Tests For Homocysteine

Prior to 1985, there already were a variety of tests used to screen for elevated homocysteine levels. These included paper or thin layer chromatography, and quantitative amino acid analysis by standard or automated column chromatography.[14] While much of the testing was performed in an effort to diagnose and elucidate the basis of one or more genetic disorders known to cause elevated homocysteine levels, the potential relationship between vitamin deficiencies and elevated homocysteine levels had already been well-recognized and discussed among experts in the field.[15]

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[13] Am. Med. Ass'n, Report 5 of Council on Scientific Affairs, *Folic Acid Relationships to Spinal Closure Birth Defects and Adult Vascular Disease* (1995) [hereinafter "AMA Folic Acid Report"]. For example, about 0.5% of the U.S. population are carriers of the mutant gene that most frequently causes inherited homocystinuria, and these carriers may demonstrate elevated plasma homocysteine levels. S. Kang et al., *Hyperhomocyst(e)inemia as a risk factor for occlusive vascular disease*, 12 Ann. Rev. Nutr. 279 (1992). Further, 20% of all vegetarians also have moderate hyperhomocysteinemia. W. Herrmann et al., *Total homocystein, vitamin B_{12}, and total antioxidant status in Vegetarians*, 47 Clin. Chem 1094 (2001).

[14] Chromatography encompasses a group of analytical chemistry methods for the separation and purification of molecules in clinical samples. In general, it involves separating the various molecules in the sample based on molecular size, chemical properties, ionic charge, relative solubility, etc.

[15] *See* S.H. Mudd, *Homocystinuria: The Known Causes, in Inherited Disorders of Sulfur Metabolism* 204, 219 (N.A.J. Carson & D.N. Raine

It also was recognized, however, that the observed association between homocysteine and vitamins B_{12} and folate, although sensitive, is not specific. "[A]n animal with elevated levels of total homocysteine is likely to have one or both [vitamin B_{12} and folate] deficiencies, but the assay [of total homocysteine] does not distinguish between the two." '658 patent col.4 ll.20-23. Both folate and B_{12} deficiencies result in hyperhomocysteinemia, thus rendering the measurement of plasma homocysteine levels an ineffective tool to *diagnose* either folate deficiency or vitamin B_{12} deficiency. It was necessary to (a) perform a second assay, for the substance methylmalonic acid, in combination with the homocysteine assay, and then (b) compare total homocysteine levels to total methylmalonic acid levels in order to diagnose and distinguish among folate deficiency, vitamin B_{12} deficiency or a deficiency of both vitamins.

Today, several newer tests are available to measure total homocysteine in body fluids and tissues. These include analysis by gas chromatography/mass spectrometry (GC/MS) as described in the Patent and fluorescence polarization immunoassay (FPI) such as the method developed by Abbott Laboratories.[16] All of these tests provide clinicians with useful information by which they can screen patients for the risk of a variety of disorders, including vascular occlusive disease. None of these tests, however, alone or in combination, can definitively diagnose a deficiency of

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eds., 1971) (citing J.G. Hollowell et al., *Homocystinuria and organic aciduria in a patient with vitamin-B_{12} deficiency*, 2 Lancet 1428 (1969)); M.C. Higgenbottom, L. Sweetman & W.L. Nyhan, *supra* note 7.

[16] GC/MS combines the features of gas-liquid chromatography (to separate molecules) with mass spectrometry, which breaks each molecule down and identifies it. FPI is based on a competitive immunoassay that uses a fluorescent label. FPI requires neither the time nor expense involved in GC/MS procedures. For details of, and comparison between these methods, *see, e.g.*, J.B. Ubbink et al., *Comparison of three different plasma homocysteine assays with gas chromatography/mass spectrometry*, 45 Clin. Chem. 670 (1999).

vitamins B_6 or B_{12}, or of folic acid, because, *inter alia*, elevated homocysteine levels may be the result of several genetic, metabolic and/or nutritional abnormalities. Relying on the observed association between hyperhomocysteinemia and vitamin levels alone is not definitive.

3. Current Use Of Homocysteine Tests And Research Into Homocysteine

Today, tests for elevated levels of homocysteine are performed for a variety of medical reasons. It is well-accepted that even a mild elevation of plasma homocysteine is an independent risk factor for cardiovascular disease, peripheral arterial occlusive disease, stroke and venous thrombosis.[17] Many studies have demonstrated the causality of homocysteine's role in the development of vascular disease and suggested benefits from dietary supplementation.[18] As

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[17] *See, e.g.*, C.J. Boushey et al., *A quantitative assessment of homocysteine as a risk factor for vascular disease. Probable benefits from increasing folate intakes*, 274 JAMA 1049 (1994). R. Clarke et al., *Hyperhomocysteinemia: an independent risk factor for vascular disease*, 324 N. Eng. J. Med. 1149 (1991). I.M. Graham et al., *Plasma homocysteine as a risk factor for vascular disease (The European Concerted Action Project)*, 277 JAMA 1775 (1997). H. Refsum et al., *Homocysteine and cardiovascular disease*, 49 Ann. Rev. Med. 31 (1998). J.M. Scott, *Homocysteine and cardiovascular risk*, 72 Am. J. Clin. Nutr. 333 (2000).

[18] AMA Folic Acid Report. *See, e.g.*, Boushey et al., *supra* note 17. S.J. Moat et al., *Treatment of coronary heart disease with folic acid: is there a future?*, 287 Am. J. Physiol. H1 (2004). M. Coffey et al., *Reducing coronary artery disease by decreasing homocysteine levels*, 23 Crit. Care Nurse 25 (2003). M.T. Stauffenberg, *Hyperhomocysteinemia measured by immunoassay: A valid measure of coronary artery atherosclerosis*, 128 Arch. Pathol. Lab. Med. 1263 (2004). *But see* M. Villar-Fidalgo et al., *Prevalence of hyperhomocysteinemia and associated factors in primary health care*, 125 Med. Clin. (Barc) 487 (2005) (suggesting the need for further research to determine whether homocysteine actually adds predictive power to measurements of cardiovascular risk).

many as 50% of patients suffering from stroke and other atherothrombotic diseases have elevated homocysteine levels.[19] Thus, plasma homocysteine levels are frequently measured to help estimate an individual's risk for one or more of these disorders.[20]

As a result of continuing investigations into, and new knowledge regarding, the relationships between levels of homocysteine and various diseases, it was estimated in 1999 that the number of homocysteine tests could grow to exceed 100 million per year.[21] The vast majority of these tests will

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[19] AMA Folic Acid Report. Am. Soc'y of Human Genetics/Am. Coll. of Med. Genetics, *supra* note 6.

[20] Recently, studies also have demonstrated an association between hyperhomocysteinemia and a number of age-related medical disorders, including cognitive impairment and Alzheimer's disease, osteoporosis-related fractures, and brain infarction, as well as the development of diabetes in certain women, and early pregnancy loss. *See, e.g.*, H.-K. Kuo et al., *The role of homocysteine in multisystem age-related problems: A systematic review*, 60 J. Gerontol. A. Biol. Sci. Med. Sci. 1190 (2005); K.L. Tucker et al., *High homocysteine and low B vitamins predict cognitive decline in aging men: the Veteran Affairs Normative Aging Study*, 82 Am. J. Cli. Nutr. 627 (2005); M. Folin et al., *A cross-sectional study of homocysteine-, NO-levels, and CT-findings in Alzheimer dementia, vascular dementia and controls*, 6(4) Biogerontology 255 (2005); R.R. Mclean et al., *Homocysteine as a predictive factor for hip fracture in older persons*, 350 N. Eng. J. Med. 2042 (2004). J.B.J. van Meurs et al., *Homocysteine levels and the risk of osteoporatic fracture*, 350 N. Engl J. Med. 2033 (2004); N.K. Kim et al., *Hyperhomocysteinemia as an independent risk factor for silent brain infarction*, 61 Neurology 1595 (2003); N.H. Cho et al., *Elevated homocysteine as a risk factor for the development of diabetes in women with a previous history of gestational diabetes mellitis: a 4-year prospective study*, 28(11) Diabetes Care 2750 (2005); W.L.D.M. Nelen et al., *Homocysteine and folate levels as risk factors for recurring early pregnancy loss*, 95 Obstet. Gynecol. 519 (2000).

[21] *American Heart Association Recommends Homocysteine Testing, at* http://www.cfonews.com/cct/c010599y.htm (last visited Dec. 14, 2005). "'It will probably soon be as common to have one's homocysteine levels

be performed to determine an individual's risk of developing heart disease or stroke. Nevertheless, the scientist or physician who views laboratory results showing hyperhomocysteinemia may, in fact, recall the association between such a result and one or more vitamin deficiencies. On that basis, the physician may, depending on the circumstances, choose to order one or more additional tests that are needed to diagnose which particular vitamin, if any, a patient may need as a supplement to his or her diet.

B. Ethical Concerns With Patents On Scientific Principles

The associations submitting this brief recognize that health-care-related patents can enhance the provision of high-quality and cost-effective medical care. The financial incentive that patents offer supports the expensive and uncertain research required to identify, test, and gain approval for new pharmaceutical products, medical devices, diagnostic testing kits, and comparable applications of scientific fact and principle that provide novel advances in medical treatment. The associations recognize that, without patent protection, many exceptionally valuable advances in medical care may not otherwise occur. In this respect, the patent system has served, and can continue to serve, patients and the medical profession well.

Patents on basic scientific principles, however, raise more difficult issues. Such patents ultimately erode the quality of patient care by limiting the knowledge physicians may use to diagnose and treat their patients.

Physicians have a longstanding ethical obligation to advance and share useful medical knowledge with patients and physicians. The principle is embodied both in Principle V of the AMA's Principles of Medical Ethics, and in Opinion 9.08 of the AMA's Code of Medical Ethics. Principle V

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checked as it is now to have one's cholesterol level checked.'" *Id.* (quoting Dr. Malinow of the Oregon Health Sciences University).

states that a "physician shall continue to study, apply and advance scientific knowledge," and "make relevant information available to patients, colleagues, and the public."[22]

Opinion 9.08 of the Code of Medical Ethics of the AMA elaborates upon this basic principle. It states, in pertinent part, that:

> Physicians have an obligation to share their knowledge and skills and to report the results of clinical and laboratory research. . . . The intentional withholding of new medical knowledge, skills and techniques from colleagues for reasons of personal gain is detrimental to the medical profession and to society and is to be condemned.[23]

Discovery of a basic scientific principle – one that could be useful to others in devising any number of useful medical applications or to a physician in reaching a diagnosis and treating a patient – is a quintessential example of the kind of medical knowledge that physicians are obliged freely to share. To interpret the patent laws to make scientific principles eligible for patent protection is not only unnecessary, but threatens to undermine, rather than promote, effective patient care. By allowing a private party to restrain the use of a basic scientific principle, patents on scientific principles hinder the efforts of others to develop or employ new and superior medical advances that would build on that principle. By creating concerns about inducing infringement, such patents deter laboratories and others from disseminating basic scientific information that would be useful to physicians in providing cost-effective and high-quality care to their

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[22] Available at www.ama-assn.org/ama/pub/category/2512.html (last visited Dec. 21, 2005).

[23] Available at www.ama-assn.org/apps/pf_new/pf_online?f_n=browse&doc=policyfiles/HnE/E-9.08.HTM (last visited Dec. 21, 2005).

patients. Such patents also interfere with a physician's ability to provide the diagnostic care a patient needs. In short, patents on scientific principles interfere with the development of medical advances and the provision of effective patient care.

SUMMARY OF ARGUMENT

Claim 13 states, in its entirety:

> A method for detecting a deficiency of cobalamin or folate in warm-blooded animals comprising the steps of:
>
> assaying a body fluid for an elevated level of total homocysteine; and
>
> correlating an elevated level of total homocysteine in said body fluid with a deficiency of cobalamin or folate.

'658 patent col.11 ll.58-65.

The Federal Circuit accepted that step one in claim 13 covers any "assay" or test for homocysteine levels, whether or not that test was described in any fashion in the specification or known in the prior art. Pet. App. 26a-27a. The Federal Circuit construed step two to "only require[] association of homocysteine levels with vitamin deficiencies." *Id.* at 8a. As a result, Claim 13 is practiced whenever a physician orders a test for homocysteine, no matter what type of test is ordered, and then considers the association of homocysteine levels with vitamin deficiency. The Court of Appeals accepted, as evidence sufficient to prove inducement, testimony that every physician who reviews results of a homocysteine test will consider the association with vitamin deficiency. *Id.* at 18a. As a result, every physician who orders and reviews the results of a test for levels of homocysteine practices Claim 13.

Claim 13 of the '658 patent improperly claims subject matter that is outside the scope permitted by 35 U.S.C. § 101. Claim 13 patents the association that any physician would

make between test results showing elevated levels of homocysteine and vitamin deficiency. Claim 13 is not limited to any particular method of testing homocysteine levels, and it does not require a physician to perform any act other than simply to order a test and read the results. Claim 13 therefore patents a scientific principle – that elevated homocysteine levels are associated with vitamin deficiency – rather than a useful application of that principle. Under long-settled limits on the permissible scope of patentable subject matter, Claim 13 is invalid.

Claim 13 also illustrates the importance of enforcing this limitation. Patents on scientific principles are precluded because they are inherently overbroad, and because they operate to chill, rather than to promote, the progress of science and the useful arts and, as in this case, the sound practice of medicine. Claim 13, as construed by the Federal Circuit, displays each of these defects. Its enforcement undercuts the objectives of the patent system as envisioned by the framers of the Constitution and as enacted by Congress.

ARGUMENT

A. Claim 13 Improperly Claims Non-Patentable Subject Matter.

The Constitution grants Congress broad power to enact legislation to "promote the Progress of Science and useful Arts, by securing for limited Times to Authors and Inventors the exclusive Right to their respective Writings and Discoveries." U.S. Const. art. I, § 8, cl. 8. Congress promptly exercised this power in the Patent Act of 1790. "[A]uthored by Thomas Jefferson," *Diamond* v. *Chakrabarty*, 447 U.S. 303, 308 (1980), the Act broadly defined the scope of matters that were subject to patent as "any new and useful art, machine, manufacture or composition of matter, or any new or useful improvement [thereof]." Act of Feb. 21, 1793, ch. 11, § 1, 1 Stat. 318, 319. Congress did not alter this language until 1952 when, in recodifying the patent laws, it

replaced the word "art" with "process." See Act of July 19, 1952, ch. 950, § 101, 66 Stat. 792, 797. Although Congress described its intent, in a Committee Report to the 1952 Act, to have Section 101 "include anything under the sun that is made by man,"[24] the inclusion of processes was not new, because the term "art" had previously been construed to include a "process." See *Diamond* v. *Diehr*, 450 U.S. 175, 182 (1981).

The scope of patentable subject matter, although broad, is not limitless. "The laws of nature, physical phenomena, and abstract ideas have been held not patentable." *Chakrabarty*, 447 U.S. at 309. As the Court has explained by illustration, "Einstein could not patent his celebrated law that $E=mc^2$; nor could Newton have patented the law of gravity. Such discoveries are 'manifestations of . . . nature, free to all men and reserved exclusively to none.'" *Id.* (omission in original) (quoting *Funk Bros. Seed Co.* v. *Kalo Inoculant Co.*, 333 U.S. 127, 130 (1948)).

Beginning in the 1850s, this Court has repeatedly held and observed that Congress has not permitted individuals to obtain exclusive ownership of laws of nature, natural phenomena, or abstract ideas. See *LeRoy* v. *Tatham*, 55 U.S. (14 How.) 156 (1852) (invalidating patent because a scientific principle is unpatentable, and all that remained was a combination of machinery known in the prior art); *Chakrabarty*, 447 U.S. at 309 (citing cases). For example, the Court invalidated the patent in *Funk* because the patentee had discovered "'only some of the handiwork of nature.'" *Id.* at 310 (quoting *Funk*, 333 U.S. at 131). By contrast, it upheld the patent in *Chakrabarty* because the patentee claimed not "a hitherto unknown natural phenomenon, but . . . a nonnaturally occurring manufacture or composition of matter." *Id.* at 309.

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[24] S. Rep. No. 82-1979, at 5 (1952), *reprinted at* 1952 U.S.C.C.A.N. 2394, 2399; H.R. Rep. No. 82-1923, at 6 (1952).

Although Claim 13 is cast in the format of a two-step "process" claim, it is indistinguishable from a scientific principle. It simply recites the fact that test results showing elevated levels of homocysteine are associated with vitamin deficiency. Claim 13 is therefore invalid because it claims subject matter that is not eligible for patent protection. That is true of each step, as well as of the claim as a whole. Claim 13 combines an abstract idea (testing, by any method) with a scientific principle (that high homocysteine levels are associated with vitamin deficiencies). Had these steps contained meaningful limitations, a valid claim might have emerged. But the Court of Appeals found no such limitation in either step.

Step one of claim 13 covers *any* test for homocysteine levels, including tests disclosed in the prior art, and tests not yet invented. It is not supported by any written description in the specification. Indeed, it is difficult to imagine how any specification could describe every method, past, present, and future, for testing homocysteine levels. Certainly this specification made no such attempt. Step one thus merely recites an "abstract idea" – that of testing for homocysteine levels – rather than a particular method for doing so.[25]

The Federal Circuit construed step two of claim 13 to cover any "association of homocysteine levels with vitamin deficiencies." Pet. App. 8a; see also *id.* at 12a. The Court of Appeals expressly refused to place any limits on the nature of that association or the acts required to establish it.

For example, the court declined to require any evaluation of the specific levels of homocysteine found, or even that homocysteine levels be elevated above some normal level or

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[25] The lack of a supporting written description can also be grounds to invalidate a claim under 35 U.S.C. § 112 paragraph 1. As discussed below, the lack of an adequate written description is characteristic of an attempt to patent abstract ideas, scientific principles, or laws of nature. *See infra* Part B.

range. Pet. App. 12a. The court also declined to require any step to confirm a diagnosis of vitamin deficiency, to identify which vitamin, if any, the patient needs, or to take any other step to associate the patient's condition with any particular "abnormalities." *Id.* at 10a. The court's construction of step two was so broad that the physician need take no step other than review the results of the test. "The correlating step *is a simple conclusion* that a cobalamin/folate deficiency exists *vel non* based on the assaying step." *Id.* at 18a (first emphasis added). The correlating step occurs automatically when the physician, aware of the "association," reads the test result. Or, to borrow from Descartes' famous maxim, "I think, therefore I" infringe Claim 13.

The Court of Appeals thus construed Claim 13 to cover a scientific principle: that elevated homocysteine levels are associated with vitamin deficiency. This fact is not part of a series of acts which form a process. It is the process. "[A] scientific truth," however, "is not a patentable invention." *Mackay Radio & Tel. Co.* v. *Radio Corp. of Am.*, 306 U.S. 86, 94 (1939). "'He who discovers a hitherto unknown phenomenon of nature has no claim to a monopoly of it which the law recognizes.'" *Diehr*, 450 U.S. at 188 n.11.

Section 101 does not permit the patenting of a basic scientific principle even when knowledge of that principle proves exceptionally helpful in treating a patient. The venerable case of *Morton* v. *New York Eye Infirmary*, 17 F. Cas. 879 (C.C.S.D.N.Y. 1862) (No. 9865), illustrates the point well. The court invalidated a patent on the seminal discovery that ether was an effective anesthetic for surgery. The court acknowledged the testimony of "distinguished surgeons" who ranked the idea of employing ether in surgery as "among the great discoveries of modern times" and lauded the patentee as one of "the greatest benefactors of mankind." *Id.* at 883. But both ether itself, and the scientific fact that inhaling ether sedates a human, were well-known. *Id.* at 882. The patent claimed no definite process for administering

ether, because the amount of ether to be given to a patient was left to the "discretion of the operator." *Id.* at 883. It thus amounted to a patent on the scientific fact that ether reduces pain during surgery which, while a useful discovery, was not patentable. *Id.*

Claim 13 is defective in the same way as the ether patent. Claim 13 identifies a useful purpose for measuring levels of homocysteine (*i.e.*, to check for vitamin deficiency), but does not claim any new method for such measuring. It fails to bring its discovery of the association of homocysteine levels and vitamin deficiency "into practical action," which is essential to patentability. *Id.* at 881-83. See *Mackay Radio*, 306 U.S. at 94 ("While a scientific truth . . . is not patentable invention, a novel and useful structure created with the aid of knowledge of scientific truth may be."); *LeRoy* v. *Tatham*, 55 U.S. (14 How.) at 175 ("The elements of the power exist; the invention is not in discovering them, but in applying them to useful objects.").

Claims 1-12 do not share this fundamental defect. Those claims recite specific methods for testing for homocysteine levels that are limited by the claim language and supported by a written description in the specification. In those claims, the patentees sought to bring "into practical action" their discovery about the association between homocysteine levels and vitamin deficiency. By devising and claiming a new method for testing homocysteine levels, they at least facially sought to claim patentable subject matter.

In Claim 13, however, the patentees overreached. They attempted to patent any physician's consideration of a scientific principle: that a patient's test results showing elevated homocysteine levels are associated with vitamin deficiency. A scientific fact – even if it is quite useful – is not patentable subject matter. For this reason, claim 13 is invalid.

B. Claim 13 Is Overbroad.

One important reason why patents on natural phenomena, scientific principles, and abstract ideas have long been held outside the scope of patentable subject matters is that such patents are inherently overbroad. They claim any method of using a fact or idea for a given purpose. Yet their specifications do not, and cannot, purport to describe all such methods. Such claims are now often rejected as lacking a written description sufficient to support the claim "under the first paragraph of § 112." *In re Hyatt*, 708 F.2d 712, 715 (Fed. Cir. 1983). Claim 13 properly should have been invalidated under this provision as well. The problem of overbreadth is inherent in a patent on a scientific principle or abstract idea.

The most famous example is *O'Reilly* v. *Morse*, 56 U.S. (15 How.) 62 (1853).[26] At issue was Samuel Morse's patent on the electro-magnetic telegraph – a patent remarkably similar in its sequence of claims to the patent at issue here.

The first seven claims of Morse's patent claimed a specific apparatus and process for a telegraph. These claims were upheld. In the eighth claim, however, Morse sought more broadly to patent "'the use of the motive power of the electric or galvanic current, which I call electro-magnetism, *however developed* for marking or printing intelligible characters, signs, or letters, at any distances.'" *Id.* at 112 (emphasis added). The Court invalidated this claim.

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[26] Another well-known example is *Wyeth* v. *Stone*, 30 F. Cas. 723 (C.C.D. Mass. 1840) (No. 18,107) (Story, J.). There the patentee invented one method of cutting ice blocks of a uniform size other than by hand, but sought to claim any such method. The court held that "[s]such a claim is utterly unmaintainable in point of law." *Id.* at 727. "No man can have a right to cut ice by all means or methods, or by all or any sort of apparatus, although he is not the inventor of any or all of such means, methods, or apparatus." *Id.*

The Court recognized that Morse's eighth claim, if allowed, would effectively grant Morse ownership of the idea of using electric current to print at a distance. That is because, under claim 8, it "matter[ed] not by what process or machinery the result is accomplished." *Id.* at 113. Claim 8 would thus cover the work of "some future inventor" who, "in the onward march of science, may discover a mode of writing or printing at a distance by means of the electric or galvanic current, without using any part of the process or combination set forth in plaintiff's specification." *Id.* Such an invention "may be less complicated – less liable to get out of order – less expensive in construction," and yet if covered by this patent might not be made available to the public. *Id.* It would give Morse "an exclusive right to use a manner and process which he has not described and indeed had not invented, and therefore could not describe when he obtained his patent." *Id.*

The same problem of overbreadth that led to the invalidation of Morse's eighth claim should also invalidate claim 13 of the '658 patent. The patentees here in claim 13, like Morse in claim 8, have written claims so broadly that they swallow all the claims that precede them. "Indeed, if the eighth claim of the patentee can be maintained, there was no necessity for any specification, further than to say that he had discovered that, by using the motive power of electro-magnetism, he could print intelligible characters at a distance." *Id.* at 119. Similarly, if claim 13 is maintained as construed, then there is no need for such claims as 1-12 or any specification, other than to say that the patentees had discovered, by measuring homocysteine levels, that they could detect a vitamin deficiency.

The basic defect in the claim challenged in each case is the same. Like claim 8 of Morse's patent, claim 13 of the '658 patent grants the patentees exclusive rights in a process they neither described nor invented. Just as Morse was not permitted to patent any method for using electric current to

send telegrams, these patentees ought not be permitted to patent any method for using homocysteine levels to determine a vitamin deficiency.

C. Patents Solely On Scientific Facts Stifle Innovation And Conflict With Patient Care.

There is a final basic reason why scientific facts, without more, have properly been deemed outside the scope of patentable subject matter. Basic scientific facts, untethered to a novel application, "are part of the storehouse of knowledge of all men." *Funk Bros. Seed Co.* v. *Kalo Inoculant Co.*, 333 U.S. 127, 130 (1948). They are elements of useful inventions, not inventions in themselves. Ensuring wide dissemination and free access to such facts is therefore essential to scientific progress.

The discussion above of the history of research into homocysteine illustrates that these patentees are neither the first nor the last to consider the relationship of homocysteine to human health. Others recognized that elevated homocyst(e)ine levels were associated with a vitamin deficiency before the patentees did, see *supra* p. 8 and note 12 and p. 9 and note 14, and the ability to test for homocysteine levels was also well-established, see *supra* p. 9. Since the patentees' work, other scientists have made, and continue to make, important contributions to our ability to measure levels of homocysteine and our understanding of its significance as an indicator of various diseases and conditions. See *supra* pp. 10-12 and notes 16-20. The range of important and ongoing research is vast, and the need for ready access to and ability to use basic facts, such as a relationship between levels of an amino acid and vitamins, is essential to those efforts. Allowing private parties to own such facts stifles scientific progress and obstructs patient care.

Here, for example, disclosure of the scientific fact that vitamin deficiencies (and, more importantly, heart disease and other conditions) are associated with elevated levels of

homocysteine created an incentive for laboratories to develop new, fast, and inexpensive ways of testing for homocysteine. But if the person who discovers such an association is permitted to patent any means of testing for it, then that patentee may "shut[] the door" to the development or use of such new tests, and discourage further research and development. *Morse*, 56 U.S. (15 How.) at 113.

This case also shows how the patentee may go further still to render unlawful the dissemination of those basic facts. Here, for example, the Court of Appeals held that petitioner had induced infringement through the publication of medical articles. Without evincing any concern, the court states:

> LabCorp publishes both Continuing Medical Education Articles as well as a Directory of Services that are specifically targeted to the medical doctors ordering the LabCorp assays. These publications state that elevated total homocysteine correlates to cobalmin/folate deficiency and that this deficiency can be treated with vitamin supplements. LabCorp's articles thus promote total homocysteine assays for detecting cobalamin/folate deficiency.

Pet. App. 15a. According to the Court of Appeals, therefore, a laboratory can induce infringement of a patent – and thereby expose itself to millions of dollars in damages and penalties – simply by informing physicians, in an article for continuing medical education, that high levels of an amino acid signal a risk to patient health. Such a ruling obviously chills the dissemination of basic facts – which, as shown above, is central to sound medical practice, and is essential for physicians to stay abreast of continuing homocysteine-related research. See *supra* pp. 13-15. Yet a fundamental objective of the patent system, and a principle reason why society is willing to confer a patent monopoly, is to promote the publication of inventions.

The Federal Circuit's ruling, if allowed to stand, would support the patent eligibility of other claims that would distort patent law beyond recognition. By discovering a previously unknown correlation between obesity and illness, for example, a researcher could obtain a patent on the process of stepping on a scale and thinking of that illness. Any entity that made or sold scales, and that dared to mention that correlation in a brochure, would then be liable for intentionally inducing infringement. Such a result is unthinkable – except under the logic of the decision below.

A final indication that the Court of Appeals erred is in the inability of any physician who knows of the association between homocysteine and vitamin deficiency to avoid practicing claim 13.[27] There can be no design around a scientific fact. For example, the patentees are able to hinder the use of homocysteine tests even when, as shown above (see *supra* pp. 11-13), the purpose is to test for a risk factor for heart disease rather than for vitamin deficiency.

A physician who learns – from the medical literature, colleagues, continuing medical education, or other public sources – of the naturally occurring association between homocysteine and vitamin deficiency cannot put that knowledge out of mind. Knowledge of basic scientific facts such as a correlation between a test result and a possible disease state is essential to the practice of medicine. Once learned, such knowledge remains.

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[27] Congress has exempted physicians from liability for direct infringement for "the performance of a medical or surgical procedure on a body," but not for "the practice of a process in violation of a biotechnology patent." 35 U.S.C. § 287(c)(2)(A). Section 287(c)(4) is, by its own terms, inapplicable to patents with applications filed prior to September 30, 1996. The '658 patent application was filed in 1986. Thus, the question of whether a physician who requests a test of a bodily fluid, and then considers the results in the light of medical knowledge, thereby performs "a medical procedure . . . on a body" within the meaning of § 287(c)(2)(A) was not addressed below and is not before this Court.

Thomas Jefferson aptly described this difficulty in allowing patents upon ideas:

> If nature has made any one thing less susceptible than all others of exclusive property, it is the action of the thinking power called an idea, which an individual may exclusively possess as long as he keeps it to himself; but the moment it is divulged, it forces itself into the possession of every one, and the receiver cannot dispossess himself of it. [28]

Nor should he. A physician is ethically obliged to consider test results in light, among other things, of current medical knowledge. Such is the nature of a scientific fact: Once known, it must be considered. And as it must be considered, it ought not be patentable.

Respect for our nation's patent laws and the developments that they have promoted should not lead to an extension of those laws to confer a statutory monopoly that Congress did not intend. In *62 Cases of Jam* v. *United States*, 340 U.S. 593, 600 (1951), this Court stated that: "In our anxiety to effectuate the congressional purpose of protecting the public, we must take care not to extend the scope of the statute beyond the point where Congress indicated it would stop." Similarly here, this Court should take care not to extend the scope of subject matter eligible for a patent beyond the point that Congress indicated that it would stop.

As this case demonstrates, upholding a claimed patent on a scientific fact would directly undercut the goal of making diagnostic and treatment advances widely accessible at minimal cost to patients. This would be an unfortunate result if Congress had so ordained. But it is without warrant where,

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[28] Letter from Thomas Jefferson to Isaac McPherson (Aug. 13, 1813) *reprinted in* The Letters of Thomas Jefferson: 1743-1826, *available at* Electronic Text Center, University of Virginia Library.

as here, Congress did not write the patent laws to permit such consequences.

CONCLUSION

For the foregoing reasons, the judgment should be reversed.

Respectfully submitted,

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